# Complete Summary

## GUIDELINE TITLE

The role of Bevacizumab (Avastin™) combined with chemotherapy in the treatment of patients with advanced colorectal cancer: a clinical practice guideline.

## BIBLIOGRAPHIC SOURCE(S)

Welch S, Kocha W, Rumble RB, Spithoff K, Maroun J, Gastrointestinal Cancer Disease Site Group. The role of bevacizumab (Avastin) combined with chemotherapy in the treatment of patients with advanced colorectal cancer. Toronto (ON): Cancer Care Ontario (CCO); 2005 Dec 12. 23 p. (Evidence-based series; no. 2-25). [18 references]

## GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

## ** REGULATORY ALERT **

## FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- September 26, 2006, Avastin (bevacizumab): Revisions to the WARNINGS and ADVERSE REACTIONS sections of the prescribing information.

## COMPLETE SUMMARY CONTENT

## SCOPE

### DISEASE/CONDITION(S)

Advanced colorectal cancer

### GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

### CLINICAL SPECIALTY

Oncology

### INTENDED USERS

Physicians

### GUIDELINE OBJECTIVE(S)

To evaluate if adult patients with advanced (locally advanced non-resectable or metastatic) colorectal cancer who are considered candidates for systemic therapy should receive bevacizumab (Avastin™) combined with cytotoxic chemotherapy

### TARGET POPULATION

Adult patients with advanced colorectal cancer who are considered candidates for systemic therapy

### INTERVENTIONS AND PRACTICES CONSIDERED

5-fluorouracil (5-FU) based chemotherapy regimen plus bevacizumab for first or second line therapy

### MAJOR OUTCOMES CONSIDERED

- Overall survival
- Progression-free survival
- Response rate

## METHODOLOGY

### METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

### DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Entries to MEDLINE (1996 to May 2005), EMBASE (1996 to week 22 2005), and Cochrane Library (2005, issue 2) databases and abstracts and presentations published in the proceedings of the annual meetings of the American Society of Clinical Oncology (ASCO) (2002 through 2005) and the American Society for Therapeutic Radiology and Oncology (ASTRO) (2002 through 2004) were systematically searched for evidence relevant to this evidence-based series.

The Medical subject heading (MeSH) search terms "bevacizumab," "avastin," "colorectal neoplasms," "randomized controlled trials," "meta-analysis" "evidence-based medicine," and "review literature" were combined with the same terms used as keywords. Additional keyword search terms used were "phase 2," "phase II," and "systematic review". Relevant articles and abstracts were selected and reviewed by two reviewers and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guidelines Clearinghouse (http://www.guideline.gov) were searched for existing evidence-based practice guidelines.

#### Study Selection Criteria

##### Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published abstracts of:

1. Randomized controlled trials (RCTs) that include bevacizumab (Avastin™) in the experimental arm in the treatment of adult patients with advanced colorectal cancer. These studies generally compared bevacizumab plus chemotherapy to the same chemotherapy regimen alone. Overall survival, progression-free survival, and/or response rate had to be reported.
2. Phase II trials reporting on bevacizumab (Avastin™) in addition to chemotherapy in the treatment of adult patients with advanced colorectal cancer. Overall survival and/or response rate had to be reported.

##### Exclusion Criteria

The following were not considered for inclusion in this report:

1. Phase I studies, because of the availability of RCTs.
2. Abstracts presenting preliminary or interim data.

3. Letters and editorials.
4. Papers published in a language other than English.

## NUMBER OF SOURCE DOCUMENTS

Two randomized phase III clinical trials and two phase II clinical trials comparing chemotherapy to chemotherapy plus bevacizumab were included in this review. Two single-arm phase II trials of bevacizumab in combination with chemotherapy were also reviewed.

## METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

## RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

## METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Systematic Review with Evidence Tables

## DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

### Synthesizing the Evidence

Where possible, the data were pooled to estimate the overall effect on survival of chemotherapy with bevacizumab versus chemotherapy alone. Pooling of survival data was performed at one year. When actual survival percentages were reported, the reported data were used in the pooled analyses. When survival percentages were not reported, data were estimated from Kaplan-Meier survival curves. The study results were pooled using Review Manager 4.2.7 (RevMan Analyses 1.0.2; version date: May 2004; © 2004 the Cochrane Collaboration), which is freely available through the Cochrane Collaboration. Results are expressed as relative risk ratios, where relative risk <1.0 favours the experimental treatment and relative risk >1.0 favours control, and a relative risk equal to 1.0 indicates no difference in risk between groups. The random effects model was used for meta-analysis as it provides the more conservative estimate of effect.

## METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

## DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The practice guideline report review was developed by the Cancer Care Ontario Program in Evidence-based Care (PEBC) using the methods of the Practice Guidelines Development Cycle. The evidence selection, approval and review was

led by two members of the PEBC's Gastrointestinal Cancer Disease Site Group (DSG) and consensus on the interpretation of the evidence and the draft recommendations were reached by the entire membership.

### RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

### COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

### METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

### DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Feedback was obtained through a mailed survey of medical oncologists in Ontario. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The survey was mailed out on September 27, 2005. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Disease Site Group (DSG) reviewed the results of the survey.

The final Evidence-based Series report was reviewed and approved by the Program in Evidence-based Care (PEBC) Report Approval Panel, which consists of two members including an oncologist, with expertise in clinical and methodology issues.

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

- For patients with advanced colorectal cancer receiving 5-fluorouracil (5-FU)-based chemotherapy as first-line therapy, the addition of bevacizumab, at a dose of 5 mg/kg every two weeks, is recommended to improve overall survival in patients with no contraindications to bevacizumab. The addition of bevacizumab to 5-FU-based chemotherapy is also recommended for patients with advanced colorectal cancer receiving second-line therapy if they did not receive bevacizumab as part of their initial treatment.
- The decision to include bevacizumab in 5-FU-based regimens requires discussion with the patient regarding risks of added toxicity and potential benefit.
- The role of continuing bevacizumab after disease progression on a bevacizumab-containing regimen is not clear due to the absence of evidence. Therefore, the continuation of bevacizumab in patients who have progressed on this therapy cannot currently be recommended outside of clinical trials.

## CLINICAL ALGORITHM(S)

None provided

# EVIDENCE SUPPORTING THE RECOMMENDATIONS

## TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials.

# BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

## POTENTIAL BENEFITS

- A phase III trial compared 5-fluorouracil (5-FU) with irinotecan (IFL) plus placebo to IFL combined with 5 mg/kg of bevacizumab every two weeks in patients previously untreated for advanced colorectal cancer. Patients randomized to IFL combined with bevacizumab had improved median overall survival (OS) (20.3 versus [vs.] 15.6 months; p=0.00003), median progression-free survival (PFS) (10.6 vs. 6.2 months; p<0.00001), and overall response rate (RR) (45% vs. 35%; p=0.0029) compared with IFL alone.
- A third arm of that trial used 5-FU/folinic acid (FA) plus 5 mg/kg of bevacizumab every two weeks, without irinotecan. That arm was discontinued after the combination of bevacizumab and irinotecan was proven safe. The subsequent analysis of the patients randomized to that arm revealed comparable outcome measures to IFL alone (median OS: 18.3 months; median progression-free survival: 8.8 months; RR 39%).
- A second phase III trial, published in abstract form, compared 5-FU with oxaliplatin (FOLFOX4) to FOLFOX4 plus bevacizumab in the second-line treatment of patients with advanced colorectal cancer. FOLFOX4 plus bevacizumab, 10 mg/kg every two weeks, was associated with a statistically significant increase in median overall survival (12.5 versus 10.7 months; p=0.0024) compared to FOLFOX4 alone.
- Randomized phase II trials have demonstrated that 5-FU/FA plus bevacizumab is associated with improved median survival, improved median time to progression (TTP), and improved response rates compared to 5-FU/FA alone. When the addition to 5-FU/FA of a 5 mg/kg dose of bevacizumab, given every two weeks, was compared with the addition of a 10 mg/kg dose at the same schedule, the lower dose was associated with improved outcome (median overall survival: 21.5 vs. 16.1 months; median time to progression: 9.0 vs. 7.2 months; response rate 40 vs. 24%).

## POTENTIAL HARMS

- In a phase III trial, 5-fluorouracil (5-FU) with irinotecan (IFL) combined with bevacizumab had comparable toxicity to IFL alone, with an increase in the incidence of grade 3 hypertension (10.9% vs. 2.3%) being the lone exception.

- The combination of 5-FU with oxaliplatin (FOLFOX4) plus bevacizumab was well tolerated; however, there was a statistically significant increase in grade 3 or 4 toxicity with the combination compared to FOLFOX alone.
- The addition of bevacizumab to chemotherapy was associated with significant but manageable toxicity, specifically hypertension, bleeding, thrombosis, and proteinuria.

## CONTRAINDICATIONS

### CONTRAINDICATIONS

Contraindications to the use of bevacizumab include cerebral metastases, uncontrollable hypertension, and severe proteinuria. Bevacizumab should not be administered to patients with advanced atherosclerotic disease, bleeding diatheses, or those with non-healing wounds, recent surgery or trauma (i.e., within the previous 28 days), since those patients were excluded from enrollment in clinical trials using bevacizumab.

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

- Data from available randomized clinical trials have demonstrated a significant advantage with the addition of bevacizumab to several 5-fluorouracil (5-FU)-based regimens, including regimens of 5-FU/folinic acid (FA), 5-FU with irinotecan (IFL), and 5-FU with oxaliplatin (FOLFOX4). These studies have included regimens using 5-FU given by bolus and by infusional means. Survival benefit has been shown with the addition of bevacizumab to both first- and second-line chemotherapy. A reasonable conclusion is that bevacizumab in combination with all 5-FU-based chemotherapy is more effective than all 5-FU-based chemotherapy alone.
- Given the data supporting the addition of bevacizumab to 5-FU with irinotecan(IFL) and to FOLFOX, the Disease Site Group (DSG) finds the addition of bevacizumab to 5-FU, folinic acid, and irinotecan (FOLFIRI) reasonable, despite the fact that this combination has not been formally evaluated in the clinical trial setting. This guideline reflects previous recommendations supporting the use of FOLFIRI over IFL.
- As there are no reported trials demonstrating the efficacy or safety of bevacizumab with oral 5-FU treatments, such as capecitabine, that combination is currently not recommended outside of clinical trials.
- The weight of evidence supports the use of bevacizumab with 1st-line chemotherapy for patients with advanced colorectal cancer. Although the evidence is less compelling for its use with 2nd-line chemotherapy, this treatment is recommended if bevacizumab is not included in the initial treatment regimen.
- FOLFOX plus bevacizumab has only been evaluated in the second-line setting. Should oxaliplatin be available, and administered, to patients in the first-line setting, the DSG finds it reasonable to include bevacizumab in order to improve survival.

### General Disclaimer

- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the evidence-based series is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any for their application or use in any way.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Living with Illness

### IOM DOMAIN

Effectiveness

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

Welch S, Kocha W, Rumble RB, Spithoff K, Maroun J, Gastrointestinal Cancer Disease Site Group. The role of bevacizumab (Avastin) combined with chemotherapy in the treatment of patients with advanced colorectal cancer. Toronto (ON): Cancer Care Ontario (CCO); 2005 Dec 12. 23 p. (Evidence-based series; no. 2-25). [18 references]

### ADAPTATION

Not applicable: The guideline was not adapted from another source.

### DATE RELEASED

2005 Dec 12

### GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

### GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

## SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

## GUIDELINE COMMITTEE

Provincial Gastrointestinal Cancer Disease Site Group

## COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

## FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Authors of this evidence-based series were polled for conflicts of interest. No conflicts were declared.

## GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

## GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

## AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- The role of Bevacizumab (Avastin™) combined with chemotherapy in the treatment of patients with advanced colorectal cancer: a clinical practice guideline. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2005 Dec. Various p. (Practice guideline; no. 2-25). Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.


### PATIENT RESOURCES

None available

### NGC STATUS

This summary was completed by ECRI on May 4, 2006. The information was verified by the guideline developer on June 1, 2006. This summary was updated by ECRI on September 29, 2006 following the FDA advisory on Avastin (bevacizumab).

### COPYRIGHT STATEMENT



## DISCLAIMER

### NGC DISCLAIMER

Date Modified: 10/2/2006